The Wildlife/Human Connection: Modernizing Risk Decisions

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This article proposes that genetic and molecular ecotoxicology can play an important role in making policy and risk assessment decisions concerning xenobiotics. It calls for a greater awareness by ecotoxicologists to the effects in wildlife and humans resulting from transgenerational exposure to synthetic chemicals that interfere with gene expression and differentiation. The difficulty of recognizing these effects on the endocrine, immune, and nervous systems in developing embryos is described and suggests why effects of this nature have traditionally not been addressed when determining risk to synthetic chemicals. Specific examples are cited of environmental effects on hormonally responsive tissue in wildlife populations which could be used as models for assessing human exposure to synthetic chemicals. Evidence is presented that the environmental load of synthetic chemicals has reached critical levels at which wildlife and human health are at risk. — Environ Health Perspect 102(Suppl 12):55–59 (1994)

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Introduction

This article presents examples of environmental effects on hormonally responsive tissue in troubled wildlife populations that provide a model for assessing previously overlooked human health hazards associated with exposure to synthetic chemicals. The difficulty of recognizing these effects on the endocrine, immune, and nervous systems in wildlife and humans explains why the problems are usually not discovered until they become quantifiable at the population level. In the past, health effects of this nature were not addressed when determining the safety of synthetic chemicals. Consequently, endocrine-disrupting, synthetic chemicals once considered benign are now an integral part of the global ecosystem posing an emerging threat to biodiversity.

The number of synthetic chemicals that are capable of disrupting the endocrine system continues to grow as they are serendipituously (*1,2*) or deliberately (*3*) discovered. Among the chemicals are fungicides, insecticides, herbicides, components in plastics and detergents, and other industrial products and by-products (*4*). These manmade chemicals look like, or interfere with, endogenously produced hormones, neurotransmitters, growth factors, and inhibiting substances. They invade the environment of the embryo and change its course of development (*5*). Effects not often expressed overtly in the parent are manifested as second generation sequelae of changes in the architecture and function of the endocrine, immune, and nervous systems of offspring exposed during critical periods of organ development (*5*).

A number of the endocrine disruptive effects reported in wildlife populations have been replicated in confined wild animals (*6,7*) and laboratory animals using single xenobiotics (*3,8*). However, in the real world, exposure involves multiple xenobiotics making causal links difficult. The effects are not necessarily expressed as gross physical defects that are visibly recognizable, but instead are expressed as losses of function which until recently have not been described. Consequently, with wildlife and humans alike, a generation may pass before the effects become apparent, and only after the problem is widespread and has reached population proportion (*9,10*).

Many of the persistent endocrine-disrupting xenobiotics are found in the reproductive tissues of animals, including humans (*11*). However, recent findings that only one, very low, dose of dioxin administered during gestation can change the sexual development of rat offspring demonstrate that a xenobiotic need not be persistent nor bioaccumulative to interfere with the development of vital systems. Timing of exposure during gestation is critical (*8*). These recent dioxin studies also emphasize the importance of broadening testing protocols for all chemicals destined to become a part of commerce that will come in contact with large numbers of wildlife and humans. Short-lived chemicals that "hit and run" might never be linked with *in utero* damage unless they are carefully screened via multigenerational studies designed to detect functional changes. Unfortunately, the current substitutes for the older, more persistent bioaccumulative chemicals, such as the DDT and PCB analogs, have not been screened for their disruptive effects on the differentiation of organ systems.

Wildlife

A comprehensive review of the literature on the health status of birds, fishes, mammals, and reptiles in the northern hemisphere reveals widespread instability, decline, and extirpation among populations (*12,13*). Among those animals that can reproduce, however, aberrant development expressed in their offspring often goes unseen because the young are kept in seclusion, making it difficult to build a case for research in functional teratology. To date, some of the most convincing wildlife research on transgenerational loss of function has been accomplished during the breeding season among nesting colonies of egg-laying species [(*14*); T Gross, L Guillette, personal communication, re: turtles and alligators]. Compared with the geographic scope and seriousness of the problem, however, there has been little support for research to determine the cause of the problems. Perhaps this is because infertility among adult animals that leads to population attrition is difficult to detect and does not catch the interest of public health authorities and funding sources compared with more obvious diseases such as cancer.

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Follow-up studies on troubled wildlife populations have revealed a number of conditions associated with reproductive success. Depending upon the species and study designs, these have been measured as reductions in embryo hatchability (*15*) and viability (*16*); chick (*17*) and fry survivorship (*18*); egg size and numbers (*19*); numbers of animals reaching sexual maturity (*20*); production of endogenous hormones, such as thyroid hormones (*7,21*), estrogen (*22*), testosterone (*23,24*), and retinols (*7*), as well as immune-competency. Increases in thyroid (*25*) and liver size (*17*); liver enzyme induction (*17*); highly carboxylated porphyrins (*26*); numbers of animals exhibiting sex reversal (*6,27,28*); spontaneous abortions (*29*); hermaphroditism (*30*); sex-linked birth defects; assymetrical brains (*31*) and skulls (*32*); and unusual behavior (*17,33*) have been reported as well. Regarding sex-linked birth defects, M Fry (personal communication) has reported that in a study of crossed-billed double-crested cormorants, the birth defects all were in phenotypic females ($n = 100$). In another study, of crossed-billed bald eagles discovered in 1993, all birth defects were in females (T Kubiak, personal communication; $n = 3$).

The above effects are not the result of mutations, but are epigenetic in nature. They are the result of changes in gene expression through many mechanisms, such as blockage, modulation, or improper timing, the results of which are unpredictable in most cases (*34*). Scientists and regulators have sought mutational answers to the problem because of the need for quantifiable standards for regulatory purposes and to respond to society's fixation on cancer. However, current standards and testing protocols for synthetic chemicals need to be reevaluated, opening new research opportunities for molecular and genetic ecotoxicologists. Obviously more needs to be learned about the mechanism of action of endocrine disruption.

The large-scale mortality among dolphin, porpoise, seal, and whale populations commencing in 1987 (*35–38*) has generated a number of questions. Why, suddenly in one year in widely disconnected geographic regions in the northern hemisphere should this occur? In this case, long-lived, toothed mammals that are obligate fish-eaters exhibited symptoms of immune incompetency and were affected by new strains of viruses (one specific to dolphins, another to seals, and another to porpoises) or by naturally produced marine toxins (*39*).

In an effort to explain the sudden onset of marine mammal die-offs, it is important to keep in mind that mature animals in the first generation exposed to xenobiotics generally do not display obvious effects as a result of their exposure (*40*). If the transgenerational hypothesis holds, wide-scale immune incompetency would not appear until the second generation (*41,42*). Were those mammals that succumbed in the recent die-offs second generation individuals whose endocrine and immune systems were constructed differently because of *in utero* exposure to xenobiotics? And were some of the older animals that died individuals whose immune systems had reached threshold levels of effect as the result of years of high-dose exposure? These animals held some of the highest concentrations of organochlorine chemicals ever reported (*43*).

The Human Connection

Table 1 provides an historical perspective on widespread exposure to xenobiotics for humans, a long-lived species, and may provide a clue to the marine mammal problem. PCBs were first manufactured and used in 1929, DDT in 1938. The 1940s are often referred to as the birth of the chemical revolution, driven by new technology during and immediately following World War II (*44*). It was during this period that humans (with a generation time of approximately 20 years) were first exposed to a vast number of chemicals. By the mid-1960s these individuals began to bear children and produced the first generation of humans exposed to xenobiotics *in utero*—the first generation born with xenobiotics in their tissues. About 1980 this generation reached reproductive age.

In the case of long-lived marine mammals, the timing of the recent mass mortalities fits the above exposure model when factoring in the delay between initial production and use of xenobiotics on land and their reaching the oceans, plus the tremendous dilution factor of the marine systems. The marine mammals that suffered the die-offs have generation times of approximately 10 to 15 years and are indigenous to highly contaminated enclosed aquatic regions, such as coastal waters and the Baltic and Mediterranean seas.

In the past, human epidemiologic studies designed to determine the outcome of exposure to a xenobiotic(s) have questioned only the health of the exposed individuals. It is not surprising that many human studies have failed to link adverse health effects with exposure to xenobiotics (Type II errors). The lesson learned from wildlife reveals the importance of considering the health of the offspring of the exposed individuals. For example, when seeking causal links for loss of fertility or immune competency among cohorts, the subjects' prenatal and early postnatal exposure must be considered (in other words, what was their parents' exposure to xenobiotics?). Prenatal and perinatal exposure to xenobiotics probably have more influence on fertility than any other exposure throughout a lifetime. Functional deficits derived from *in utero* exposure in many cases may not correlate with only postnatal exposure. Most important, in light of the widespread distribution of these chemicals in the environment, it may be too late to find unexposed populations.

Evidence is building that xenobiotics are present in humans at concentrations that are toxicologically relevant. For instance, female seals exposed to 27 µg/kg/body weight (bw)/day PCB on a Wadden sea fish diet were less productive than seals exposed to 8 µg/kg (bw)/day on a North Atlantic fish diet (*45*). They experienced reduced plasma retinol and fewer implantations and were more prone to abort and develop uterine occlusions. The Wadden Sea population of seals collapsed from 3000 to 500 animals between 1950 and 1975. Female mink, animals who, like seals, also have delayed implantation, suffered similar and more severe effects when exposed to 25/µg/kg (bw)/day PCBs (*46*). Similarly, it was estimated that the mothers of children who experienced impaired visual recognition memory at 7 months and short-term memory problems at 4 years were delivering a dose of >27 µg/kg (bw)/day PCBs to their offspring (*47*). In

Table 1. Chronological examination of human exposure to synthetic chemicals.

Time span	Exposure event
1929	PCBs introduced
1938	DDT first manufactured
1940s–WWII	FIRST WIDE SCALE EXPOSURE TO MAN-MADE CHEMICALS
1940s–1950s	First generation exposed postnatally
1950s–1970s	First generation born that was exposed in womb
1970s–1990s	First generation exposed in womb reaching reproductive age

the same study it was also estimated that the mothers (from Michigan) were exposed to 0.093 µg/kg (bw)/day PCB throughout their life preceding pregnancy, which provides a model of the persistence of the PCBs. By comparison, 52.5% of Inuit women in eastern Arctic Canada participating in seven food consumption surveys are exposed to 0.25 to 3.25 µg/kg (bw)/day PCB (*48*). Suckling infants consuming breast milk at the U.S. average of 0.8 to 1 ppm PCB in milk fat are exposed to 5 µg/kg (bw)/day PCB, five times the Allowable Daily Intake (ADI) set by the Food and Agricultural Organization for a 70 kg adult (*49*). The parents of the children in the Japanese rice oil incident (contaminated with PCBs and furans) were exposed to 63 µg/kg (bw)/day PCB for three months (*50*), about 1000 times the lifetime dose of the Michigan mothers.

The average U.S. adult's body burden of dioxin (2,3,7,8-TCDD), is approximately 7 to 10 ppt. Dioxin's ability to induce cytochrome P450 enzymes in rat liver hepatoma cells (H4IIE) has been used as a surrogate to describe its toxicity. Using dioxin as the standard for CP450 activity on a weight-to-weight basis one can either measure directly or calculate (using equivalency factors times concentration) the toxicity of other dioxinlike compounds in tissue. The combined 2,3,7,8-TCDD, dioxin and furan isomers, and coplanar PCBs in the average adult's body are equivalent to 50 dioxin enzyme toxicity equivalents (TEQs). This is very close to the 64 ppt of pure 2,3,7,8-TCDD fed to pregnant rats whose male pups experienced abnormal sexual development, sperm count reduction, and behavioral changes (*8*). A recent French report found five coplanar PCB congeners (total 170 ppb) in human breast-milk fat that on an H4IIE basis are equivalent to 6397 2,3,7,8-TCDD TEQs (*51*). The breast-milk fat held 1.01 ppm total PCBs which is similar to the US average of 1 ppm. In addition, the milk held 307 ppbs of five PCB congeners [numbers 28 (*52*), 52 (*53*), 138 (*54*), 153 (*52,54*), 169 (*55*)] that also disrupt the endocrine system and reproductivity. Double-crested cormorants exhibit significant increases in embryo mortality when their eggs hold approximately 100 dioxin TEQs using the H4IIE assay, with measurable losses commencing at about 40 or 50 TEQs (*16*).

A number of laboratory studies suggest that fertility among human populations, like wildlife populations, when exposed to ubiquitous xenobiotics may be at risk. For example, in repeated trials it was demonstrated that the sperm of mature male rats exposed to PBCs postnatally through breast milk have difficulty penetrating ova or maintaining a viable zygote (*56*). In another study, pregnant rats fed one meal of dioxin [0.064, 0.16, 0.4, and 1.0 µg/kg (bw)] on day 15 of gestation gave birth to male offspring who were demasculinized and feminized, as determined by morphological, biochemical, physiological, and behavioral parameters; their sperm count was also reduced 75% (*8*). Many of the effects were not measurable until the pups matured. In a follow-up study (1.0 µg/kg bw) female pups exhibited morphological changes in external genitalia at birth and a sequalae of changes in the reproductive tract that were similar to effects reported in mice and humans exposed in utero to diethylstilbestrol (DES) (L Birnbaum, LE Gray, personal communication, 1993).

The motility of sperm from men experiencing fertility problems (<20 million sperm/ml) was inversely proportional to the concentration of three PCB congeners in their semen; 2,4,5,2′,4′,5′-hexa-(no.153), 2,4,5,2′,3′,4′-hexa-(no. 138), and 2,4,5,3′,4′-pentachlorobiphenyl (no. 114) (*53*). All three congeners are commonly found in human breast milk (*57*). Congener 153 comprises approximately 20% of the PCB body burden of people living in industrialized temperate areas and 40 to 50% of the body burden of native Americans living in eastern Arctic Canada (*58,59*). A meta-analysis that reexamined 61 sperm-count studies revealed that worldwide sperm count has decreased by approximately 50% since 1938 (*9*). A doubling of cryptorchidism occurred in the United Kingdom between 1970 and 1987 (*60,61*). Realizing that these effects could be the result of exposure to elevated endocrine-disruptors during prenatal development, it has been suggested that the cause may be from environmental contaminants (*62,63*). A significant reduction in penis size at puberty, among other problems, has been associated with prenatal exposure to PCBs and furans among the offspring of women who consumed PCB contaminated rice oil in Taiwan (*64*).

Recommendations

Wildlife and humans are signaling problems at the population level that biodiversity is at risk. Addressing the problem with laboratory animal studies on a chemical-by-chemical basis will not work. The additive (A Soto, personal communication), synergistic, and other interactive (*65*) effects of chemicals already in the environment cannot be predicted. For ecotoxicology to meet these challenges it must:

- be more aware of and develop protocols to assess functional damage in the field;
- test in the laboratory the hypotheses generated in the field concerning causal links between wildlife damage and chemicals;
- find early markers in developing tissue that predict long-term delayed effects on functionality for both wildlife and humans;
- test the hypothesis that there are links between cell differentiation during development and cancer;
- break disciplinary boundaries, reach out, and collaborate with those responsible for public health; and
- convince the policy/risk community that field data have a role in its deliberations.

With this agenda in place ecotoxicology could bring a "real-world approach" to decision tables.

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